Physiology of Breathlessness & Current Research

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Overview

• Definition & burden of breathlessness

• Physiological basis of breathlessness in health & disease
  – Role of sensory afferent feedback & neural respiratory drive

• Neural respiratory drive: the proximate cause of breathlessness intensity
  – Importance of impaired respiratory mechanics
  – Where does hypoxaemia fit in?

• Build a conceptual physiological model to understand breathlessness & treatment options

• Highlight contributions of current physiological research
The unmet burden of breathlessness

- A common, distressing symptom of cardiorespiratory disease and malignancy
- Reported by at least one in four people worldwide
- Often refractory despite best evidence-based management
- A UK-based cross-sectional study observed that treatment for breathlessness was required in 25% of emergency medical admissions

Gronseth et al., Eur Respir J, 2014
Currow & Abernethy Current opinion in supportive and palliative care, 2012
The healthy untrained respiratory system is ideally adapted for exercise

• Alveolar ventilation closely matched to metabolic demands across range of physical activities
• Leg fatigue rather than breathlessness is the dominant exercise-limiting symptom in health (cycle exercise)
• Breathlessness becomes important in “special” normal physiological states
  – Elderly
  – Pregnancy
  – Obesity
  – Athletes
• ...and when physiology is abnormal (disease)

Breathlessness

COPD

Asthma

Heart Failure

Obesity

Anxiety / Depression

Fatigue

Cancer

Anaemia

Other Conditions

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Why do patients with COPD stop?

Large surveys show 70% of patients with COPD are breathless climbing a single flight of stairs.

Rennard et al, Eur Respir J 2002
Dyspnea (breathlessness): definition

- “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity.”

- “The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioural responses.”


D Mahler. Curr Opin Support Palliat Care 2011
• From this definition, it is clear that the mechanisms of breathlessness are highly complex and multifactorial

• However, *if asked carefully*, patients can reliably distinguish and quantify:
  – the perceived *intensity* of breathlessness (sensory domain)
  – unpleasantness
  – subsequent *cognitive, emotional & behavioural* responses
  – *descriptors* e.g. air hunger, chest tightness, increased work/effort

Parshall et al., *Am J Respir Crit Care Med* 2012
Banzett et al., *Eur Resp J* 2015
Breathlessness

Breathing
- Inefficient breathing
- Increased work of breathing
- Increased respiratory rate
- Use of accessory muscles
- Dynamic hyperinflation

Thinking
- Thoughts about dying
- Misconceptions
- Attention to the sensation
- Memories, past experiences
- Anxiety, distress
- Feelings of panic

Functioning
- Deconditioning of limb, chest wall, and accessory muscles
- Reduced activity
- Tendency to self-isolate
- More help from others

Sara Booth, Cambridge BIS
Neurophysiology of breathlessness

• The “lung-brain axis”
• Subcortical & cortical integration of sensory feedback

1. Afferent feedback from sensory receptors in the respiratory system
2. Awareness of levels of neural respiratory drive to the respiratory muscles (corollary discharge)
   – Efferent copy of motor drive, transmitted to sensory cortex


D Mahler. Curr Opin Support Palliat Care 2011
Proposed respiratory afferents that modulate (increase or reduce) breathlessness

<table>
<thead>
<tr>
<th>Air flow on face</th>
<th>Trigeminal skin receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxemia</td>
<td>Carotid and aortic bodies</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>Medullary chemoreceptors</td>
</tr>
<tr>
<td>Acidosis</td>
<td>Carotid and aortic bodies</td>
</tr>
<tr>
<td>Lung inflation</td>
<td>Medullary chemoreceptors</td>
</tr>
<tr>
<td>Irritant substances</td>
<td>Slowly adapting stretch receptors</td>
</tr>
<tr>
<td>Airway collapse</td>
<td>Rapidly adapting stretch receptors</td>
</tr>
<tr>
<td>Lung congestion (e.g., edema, inflammation)</td>
<td>Airway/epithelial C-fibers</td>
</tr>
<tr>
<td>Distension of vascular structures</td>
<td>Rapidly adapting stretch receptors</td>
</tr>
<tr>
<td>Change in muscle length (e.g., distension)</td>
<td>Pulmonary C-fibers (j receptors)</td>
</tr>
<tr>
<td>Change in muscle force</td>
<td>Pulmonary/cardiac vascular receptors</td>
</tr>
<tr>
<td>Metabolic activity</td>
<td>Respiratory muscle spindles</td>
</tr>
<tr>
<td>Metaboreceptors in respiratory muscles</td>
<td>Respiratory muscle tendon organs</td>
</tr>
<tr>
<td>Alteration of breathing</td>
<td>Chest wall joint receptors</td>
</tr>
<tr>
<td>Emotions (e.g., anger/fear)</td>
<td>Limbic system</td>
</tr>
</tbody>
</table>

D Mahler. Curr Opin Support Palliat Care 2011
Neural Respiratory Drive
The proximate cause of breathlessness

Ventilatory demand:
Hypoxia
Hypercapnia
Acidosis (incl. lactataemia)
Hypoxic ventilatory drive

- Little response of carotid bodies to hypoxia until \( \text{PaO}_2 \) 55-60mmHg when normocapnic

- i.e. hypoxic ventilatory response has little role in everyday life under usual physiological conditions

- But, there is a synergistic ventilatory response if \( \text{PaCO}_2 \) is also raised
COPD

Respiratory Muscles

Load on respiratory muscles

Airways obstruction
Static & dynamic hyperinflation
Intrinsic PEEP
Increased $V_E$ (hypoxia, hypercapnia, peripheral muscle dysfunction, early lactataemia)
Increased respiratory rate
Reduced inspiratory time
/increased inspiratory flow

Hyperinflation with muscle shortening and abnormal geometry

Capacity of respiratory muscles

Neural respiratory drive

Cortex

Breathlessness
Jones, P W Thorax 2001;56:880-887

(SGRO = St George’s Respiratory Questionnaire)
Gas trapping & hyperinflation

- Restricts expansion of tidal volume, limiting ventilatory capacity
- Development of positive end-expiratory pressure imposes an inspiratory threshold load
- Functional inspiratory muscle weakness (diaphragm sarcomere shortening, length-tension relationship)
- Reduced chest wall compliance
Dynamic hyperinflation (DH) limits inspiratory capacity & tidal volume expansion during exercise in COPD

DH imposes a limit to tidal volume expansion despite increasing neural respiratory drive

Reductions in DH, eg by long-acting bronchodilators & lung volume reduction surgery, reduce NRD & breathlessness in COPD


Man WD et al., Thorax 2004
Gorman RB et al., AJRCCM 2005
Measurement of NRD: Respiratory muscle electromyography (EMG)

Multipair oesophageal diaphragm EMG (EMGdi) catheter

Parasternal intercostal muscle EMG is a non-invasive surrogate measure of EMGdi

Reilly CC et al., Thorax 2011
EMGdi in a normal subject at rest

Resting EMGdi = 8% max

EMGdi in a normal subject during maximum voluntary ventilation

EMGdi in severe COPD at rest

Resting EMGdi = 45% max

EMGdi in severe COPD during maximum voluntary ventilation

• Resting NRD is higher in COPD patients than in age-matched healthy controls

• During exercise in COPD, tidal volume expansion is limited by impaired respiratory mechanics, despite increasing NRD

Breathlessness intensity is closely related to NRD (EMGdi%max) in COPD

$r=0.98$, $p=0.0001$

Neuroventilatory uncoupling

C Jolley et al Eur Resp J 2015
interstitial lung disease (ILD)
COPD
healthy controls

NRD & breathlessness increased with mechanical constraints on breathing (VT/IC%)
NRD (EMGdi%max) – breathlessness intensity relationships preserved despite differing physiological basis for mechanical constraints

Faisal et al AJRCCM 2016
Less clear relationship between peak exercise breathlessness & SpO$_2$

<table>
<thead>
<tr>
<th>Variable</th>
<th>ILD</th>
<th>COPD</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work rate, W (% predicted)</td>
<td>91 ± 31* (56 ± 16*)</td>
<td>91 ± 33† (63 ± 20†)</td>
<td>175 ± 59 (112 ± 22)</td>
</tr>
<tr>
<td>$V_{O_2}$, L/min (% predicted)</td>
<td>1.59 ± 0.58* (68 ± 17*)</td>
<td>1.60 ± 0.53† (75 ± 18†)</td>
<td>2.68 ± 0.77 (123 ± 17)</td>
</tr>
<tr>
<td>$V_{O_2}$, ml/kg/min</td>
<td>17.3 ± 4.8*</td>
<td>19.1 ± 5.4†</td>
<td>34.2 ± 7.9</td>
</tr>
<tr>
<td>Heart rate, beats/min (% predicted)</td>
<td>127 ± 28* (74 ± 15*)</td>
<td>131 ± 22† (79 ± 13†)</td>
<td>157 ± 13 (93 ± 6)</td>
</tr>
<tr>
<td>$V_T$, L</td>
<td>60.8 ± 20.9*</td>
<td>52.8 ± 17.1†</td>
<td>97.3 ± 24.8</td>
</tr>
<tr>
<td>$V_T$/IC, %</td>
<td>1.56 ± 0.47*</td>
<td>1.44 ± 0.48†</td>
<td>2.39 ± 0.65</td>
</tr>
<tr>
<td>$F_b$, breaths/min</td>
<td>40 ± 10</td>
<td>38 ± 7</td>
<td>77 ± 8</td>
</tr>
<tr>
<td>$T_v$/Total</td>
<td>0.48 ± 0.04†</td>
<td>0.43 ± 0.06†</td>
<td>0.48 ± 0.03</td>
</tr>
<tr>
<td>IC, L</td>
<td>1.96 ± 0.58*</td>
<td>1.89 ± 0.46†</td>
<td>3.08 ± 0.78</td>
</tr>
<tr>
<td>ΔIC from rest, L</td>
<td>-0.04 ± 0.28</td>
<td>-0.28 ± 0.48</td>
<td>0.04 ± 0.62</td>
</tr>
<tr>
<td>IRV, L</td>
<td>0.39 ± 0.35*</td>
<td>0.46 ± 0.20†</td>
<td>0.69 ± 0.26</td>
</tr>
<tr>
<td>EELV, % TLC</td>
<td>50 ± 8†</td>
<td>67 ± 7†</td>
<td>47 ± 7</td>
</tr>
<tr>
<td>EILV, % TLC</td>
<td>90 ± 8</td>
<td>92 ± 5†</td>
<td>88 ± 4</td>
</tr>
<tr>
<td>$P_{ETCO_2}$, mm Hg</td>
<td>33.8 ± 5.1</td>
<td>36.5 ± 5.8</td>
<td>33.4 ± 3.9</td>
</tr>
<tr>
<td>$V_{E}$/$V_{CO_2}$</td>
<td>36.4 ± 5.8</td>
<td>32.7 ± 5.1</td>
<td>33.3 ± 4.2</td>
</tr>
<tr>
<td>SpO$_2$, %</td>
<td>89.8 ± 4.3*</td>
<td>92.3 ± 3.7</td>
<td>94.5 ± 2.5</td>
</tr>
<tr>
<td>O$_2$ pulse, ml/beat</td>
<td>12.6 ± 3.7*</td>
<td>12.5 ± 4.7†</td>
<td>17.1 ± 4.9</td>
</tr>
<tr>
<td>Dyspnea, Borg units</td>
<td>6.1 ± 3.0</td>
<td>6.2 ± 2.4</td>
<td>5.5 ± 3.3</td>
</tr>
<tr>
<td>Leg discomfort, Borg units</td>
<td>5.9 ± 2.4</td>
<td>6.4 ± 2.3</td>
<td>6.2 ± 3.3</td>
</tr>
</tbody>
</table>

Faisal et al AJRCCM 2016
Behavoural Response: Spiral of Disability

Cardiorespiratory Diseases
Malignancy

Breathlessness

Exercise training
Pulmonary rehabilitation

Muscle Deconditioning

Excess Lactate / CO₂ Production

Inactivity

Leg Fatigue
Leg Weakness

Casaburi et al., Am Rev Resp Dis 1991
Seymour et al., Thorax 2010
Respiratory muscles

Load on Respiratory Muscles

Neural Respiratory Drive

Cortex

BREATHLESSNESS

Intensity Quality

Respiratory afferents

Limbic processing

Measure: Modified Borg

Measure: EMGdi/EMGdi,max

Respiratory muscle weakness

Capacity of Respiratory Muscles

Healthy (exercise)

Lung disease

Obesity

Heart failure

Comorbidities (anaemia, hypoxia, altitude, ageing)

Modified from Jolley & Moxham AJRCCM 2016
Summary

- There is a close relationship between levels of neural respiratory drive (NRD), measured as EMGdi, and breathlessness intensity in health and chronic respiratory disease.
- Impaired respiratory mechanics are a particularly potent cause of increased NRD & breathlessness, frequently dominant over hypoxaemia as a contributor to breathlessness.
- NRD is increased by lactataemia (peripheral muscle deconditioning), importantly modifiable by exercise training.
- Patient-reported breathlessness intensity provides insights into respiratory load / NRD not always evident from conventional measures of lung function.
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